THE

Goulstonian Lectures

FOR 1874,

ON THE

ORIGIN AND RELATIONS

OF

NEW GROWTHS.

DELIVERED AT THE ROYAL COLLEGE OF PHYSICIANS,

BY

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THE ORIGIN AND RELATIONS OF NEW GROWTHS.

INTRODUCTORY LECTURE.

MR. PRESIDENT,—The title of the course of lectures which I shall have the honour of delivering before you is one so wide and comprehensive, that I must endeavour to define somewhat more precisely the limits of the subject.

The term tumour, which was, I suppose, the one first applied to the structures which I have called new growths, had once, it is needless to say, a very wide range of meaning, and even in modern times has been used with considerable laxity. With the ancients, for instance, before inflammation had been conceived of as an abstract process, the phlegmon or inflammatory swelling was put in the same category as what we should now call a cancer; nor was it then possible to separate from this class swellings produced by any cause whatever. So wide a conception would, of course, at the present day be practically useless, and is accepted by no one. But even in the most important work yet devoted to this subject, Virchow's great treatise on tumours, the corresponding German term is taken in a very comprehensive sense. Virchow includes in his work, for instance, all kinds of cysts, even hydrocele, as well as the products of tubercular and syphilitic diseases. Without any intention of fully discussing the proper definition of the word tumour or new growth, I still feel it necessary to mark out clearly the subject of the following lectures, and will therefore just say, by way of preliminary, that my remarks will be confined to those tumours which may be fairly described as new growths, omitting mere enlargements of parts already existing, and the products of inflammation, whether acute or chronic, and omitting also the consideration of syphilitic and tubercular products, as being more nearly allied to inflammation. What we include, then,

are nearly what Virchow distinguishes as pseudo-plasmen or true growths (Gewächse).

The group thus limited includes all new formations, in the form of a more or less circumscribed mass, of substance resembling the simple tissues of the body, or immature stages of them; it includes also those productions known as cancers, and various growths nearly allied to these, known as sarcomatous tumours.

Among the simple tissue-tumours, I recognise fibrous (fibroma), mucous (myxoma), fatty (lipoma), cartilaginous (enchondroma), osseous (osteoma), vascular (angioma), muscular (myoma), nervous (neuroma), glandular (adenoma), and lymphatic (lymphoma and lymphangioma). Under cancers, I include epithelial cancer or epithelioma; and, under sarcomatous tumours, several forms which approximate to simple growths. Finally, there are combinations of the forms just mentioned. I shall not attempt to define the class thus made up, except by simple enumeration. The characters of the smaller groups are tolerably well marked, and no practical difficulty need arise in knowing what kind of objects it is intended to discuss.

The chief fact which all these structures have in common is the fact of growth or increase, and, moreover, of a growth which appears to be, in a certain sense, independent of that of the body, as if the tumour had some separate life of its own. So strongly did this impress the older observers, that for a long time tumours were regarded as something parasitic, or foreign to the organism.

Harvey has expressed this conception very distinctly. After showing that embryos, once fecundated, are inspired with a soul, or *anima vegetativa* of their own, which may be taken to mean, in Harvey's philosophical language, what we should now call a separate life, "and this", he says, "when they have received, they order themselves and grow, living at their own, not their parents', command". . . . . "And in this manner", he goes on, "doe mushrooms and plants growing to trees live. We discover likewise in our own bodies, that cancers, fleshy and also phlegmatical tumours and such like swellings, are supplied and fed as it were with their own proper vegetative souls, while in the interim the live and genuine parts of the body do extenuate and wither, and that because these tumours do seduce all the aliment to themselves; and so defraud the rest of the body of its fostering juice (as of its genius) wherefore they are called phagedænæ and lupi, devouring cankers and wolves." (*Anatomical Examinations concerning Generation*, p. 153. London, 1653.)

The idea of a separate life is of course now untenable, and no one can

doubt that a tumour is essentially a part of the body; but, nevertheless, there are certain respects, both morphological and dynamical, in which tumours do separate themselves from the general unity of forces displayed in the organism. Dynamically or physiologically speaking, we may say that this departure consists in a preponderance of the vegetative, and an almost entire absence of the animal, life. No tumour or new growth exercises any specially animal functions. Their life is simply nutritive; and, if we may adopt the distinction of Mr. Herbert Spencer between the function of accumulation and that of expenditure of force, then we may say, though it seems a paradox, that tumours are like plants, in being almost wholly accumulators. This difference, also, is not without its bearings on morphology; for if expenditure or liberation of energy, which is the characteristic dynamical feature of animals, be scarcely exhibited in new growths, we may see in this fact partly the cause of their unrestrained increase in size. It has been shown by Mr. H. Spencer to be a general and almost self-evident law of organic nature, that the amount of growth depends upon the surplus of nutrition over expenditure. Growth will, then, the nutrition being equal, vary inversely as the amount of force liberated. When the expenditure is nothing, the whole of the nutrition will be applied to growth. If the expenditure of energy be very great, growth will be strictly limited.

A simple illustration may make this distinction plain. The antagonism between increase of bulk and the quantity of force evolved in different organisms is seen in the contrast between birds and mammals, or between birds and reptiles. The former, compelled by their aerial life to exert a relatively much greater amount of energy in motion, will have the less material remaining for nutrition; and the only members of the class which approach in bulk the larger mammalia and reptiles are those which, living on land, use far less energy in locomotion. Comparing birds and reptiles alone, as being the most nearly allied, we see another broad contrast in the greater amount of heat liberated in the small bodies of birds than in the comparatively bulky reptiles, as well as in the more rapid and varied motions of the former.

Applying these principles to the growth of tumours, we have, of course, to compare structures which are alike in all other respects except those points under consideration. For instance, we may contrast physiological and pathological productions of simple tissues. In the former case, the newly formed structure has what we call a function; in the latter, none. Function is, of course, not always associated with liberation of force. These are simply passive functions, like those of

the fibrous tissues and the skeleton in preserving mechanical equilibrium, or that of the fatty subcutaneous tissue in preserving the equilibrium of temperature; in these cases, there is evidently no considerable liberation of energy. Again, the precise dynamical relations of the functions of the organs of assimilation and of those of secretion are still doubtful. But in the case of muscular tissue, and in some parts, at all events, of the nervous system, liberation of energy is inseparable from the functional activity of the organ. Hence, it is only from the latter class of tissues that our illustrations can be drawn.

To illustrate our present point, we may compare, for instance, the physiological growth of muscular tissue in the uterus, during pregnancy, with the pathological production of the same tissue in the form of tumours. In early stages, we know that the process of growth is essentially the same in both cases. There is, in both, a new production of muscular fibre-cells, and the histological development appears to be identical.* The production of new tissue in the simple physiological hypertrophy of the gravid uterus, is as abundant as that in many tumours; it must, also, be equally rapid; but it reaches a certain limit, and conforms to a certain type; while the tumour, on the other hand, has no very definite limit, and shows no conformity to rule in its shape. How are these differences to be explained? Certainly not by a difference in the amount of nutriment supplied. The pregnant uterus is a structure extremely rich in vessels, and most abundantly nourished; uterine tumours, on the other hand, contain so few vessels, that the existence of the latter has been even denied altogether. The chief point of contrast seems to be that the uterus, however large, is still capable of exercising normal functions, and there will thus always be a certain liberation of force, proportional to the pressure which the organ has to sustain, even independently of the immense efforts of parturition. The muscular tissue contained in a tumour, on the other hand, although also capable of liberation of energy by contraction (for spontaneous contraction has been observed in such tumours), does not, in fact, exercise any force; its situation and relations make this impossible. Whatever nutriment, then, it receives, will all be applied to the accumulation of tissue—that is, to growth. The surplus of nutrition over expenditure will, in fact, be nearly the whole of the nutrition. What wonder, then, that such structures, once commenced, show such monstrous exaggera-

* The identity of the processes was indeed observed directly by Dr. Bristowe in the tumours of the pregnant uterus. (*Path. Trans.*, iv, 218.)

tion of growth? Dr. Bristowe has remarked, that "such tumours not only do, but must, grow during pregnancy, and must, at least, attain a bulk, the ratio of which, to the former bulk, is that of the gravid to the unimpregnated uterus." If our principle is correct, they must grow in an even higher ratio, since they lose nothing by functional activity.

An obvious test of the truth of this principle is the relative frequency of new growth in passive or actively functioning tissues respectively; and we do find, as a matter of fact, that they are incomparably more frequent in the former. Fatty tissues, bone tissues, and all the varieties of growth which originate in fibrous tissue, are instances of the connection between mechanical passivity and excessive growth. On the other hand, voluntary muscle, the dynamical tissue *κατ' ἐξοχὴν*, never gives rise to tumours, or forms a part of any, except of certain perfectly abnormal mixed growths, which more nearly resemble an abortive fœtal development. We have here, perhaps, the secret of the extraordinary rarity of tumours composed of striped muscle.

This argument might obviously be pressed too far. If taken without qualification, it would go to prove that there could be no limit to the growth of a tumour. In fact, we know, of course, that tumours do not unfrequently cease to grow, though their growth is much less clearly circumscribed than that of the normal parts of the body. They must, indeed, obey the general laws of limitation of organic growth, which laws are very clearly stated by Mr. Herbert Spencer somewhat as follows. "Growth," he says, "is unlimited, or has a definite limit, according as the surplus of nutrition over expenditure does, or does not, progressively decrease."

In the case of organisms, Mr. Spencer shows that there are certain relations which necessarily cause this surplus to decrease. That which is most applicable to the case of tumours is the following.

"Since, in similar bodies, the areas vary as the squares of the dimensions and the masses vary as the cubes, it follows that the absorbing surface will increase in a smaller ratio than the mass. If a growth like an organism increase, so that its dimensions are doubled, the absorbing surface will be only four times what it was, while the mass has become eight times as great. It follows, then, the ratio of nutriment absorbed to mass will become less and less, while, if there be any expenditure of force whatever in the mass, this will come, in the end, to more than balance the nutrition. The supply of nutrition over expenditure will at least become zero, and growth will be arrested."

Now, in tumours, the absorbing surface is, of course, represented by

the inner surface of the blood-vessels, and this would, of itself, be sufficient to show that the growth of tumours cannot be really unlimited. In special cases, too, particular causes, such as the condition of the vessels, the relation to other parts, will have their effect; but, notwithstanding all this, the broad distinction will remain that, while organs of the body reach only a definite size, and then remain stationary, the growth of tumours is limited by no rigid law; their growth being like the growth of a tree, rather than like the growth of an animal. In fact, if we may, for the moment, speak of a morbid growth as an organism, the following statement of the law of limitation, in Mr. Spencer's words, will be strictly true.

"In the same organism, the surplus of nutrition over expenditure is a variable quantity, and growth is unlimited, or has a definite limit, according as the surface does, or does not, progressively decrease. This proportion is exemplified, on the one hand, by the increasing growth of organisms that do not expend force, by the growth, slowly diminishing, but never completely ceasing, of organisms that expend comparatively little force, and by the definitely limited growth of organisms that expend much force. On the other hand, this law follows from a certain relative increase of expenditure that necessarily accompanies increase of bulk, and is, therefore, an indirect corollary from the persistence of force."

The aspect of new growth just considered has perhaps been too much neglected, but greater importance will always attach to the morphological aspect, and that I now propose to consider.

For the formation of tumours or new growths, I have been able to arrive at no better definition than this: the addition to an organism, which is in its general outlines already completed, of new parts without any definite function. Such a process must be—in the case of highly organised animals, at all events—one extremely abnormal. To explain it all, we must have recourse to the method of a comparison, and endeavour to find out what better known processes it most resembles, and what, on comparing it with each of these successively, are the points of likeness and the points of contrast.

It appears that there are three processes much more commonly met with in living bodies with which the production of tumours may advantageously be compared. These are the formation of parts in the incomplete embryonic organism; the reproduction of parts worn out or lost in the complete organism; and, finally, the enlargement of parts already existing. Of these three processes—embryonic development, repair,

and hypertrophy—each possesses some points of contact with the processes of which we are to speak ; in fact, so gradual is the transition in some cases from each of them to tumour-formation, that it may be difficult to know what term we ought to apply. The transition from embryonic development to tumour-formation is seen, for instance, in the occurrence of congenital tumours. Sometimes, as in the peculiar congenital tumours from the sacral region, a continuous series may be traced from a comparatively simple cystic structure through teratoid forms, gradually increasing in complexity up to a complete twin fœtus, or " pygodidymus".

The transition from repair to tumour-formation is also quite gradual. It is seen, on the one hand, in such structures as granulations, which would be called new growths, had they a more permanent existence ; and in such growths as cicatricial keloid of the skin, which, though ultimately tumours, start from a scar.

Finally, that there are numerous transitions from hypertrophy to tumour-formation is a fact so generally recognised, that it need hardly be insisted upon as a general principle, though certain special cases will afterwards be discussed. It seems, then, worth while to follow out the three lines of comparison here suggested, and to see how far the formation of tumours agrees with or differs from each of these processes. In making these comparisons, I shall, in the first place, confine myself chiefly to the consideration of tumours which resemble the simple tissues of the body, since the formation of each of these must of course be more nearly paralleled by physiological formations than the malignant heterologous growths, such as cancer and sarcoma ; but it is not always possible to draw the line, and I hope to show in subsequent lectures that the same principles which apply to the one class of tumours apply also to the other.

Comparison of Tumour-Growth with Embryonic Growth.

The most striking features of embryonic growth may perhaps be set down as follows. There is, according to the great law of Von Baer, progress from the general to the special, with ever increasing differentiation of parts—so that it is, in fact, development or increase of structure, not merely growth or increase of size. The amount of growth is limited by some general law of the organism, and we can predict beforehand with tolerable certainty what size will be ultimately attained. The form of growth is also limited, or, so to speak, predetermined in the same way, so as to be susceptible of prediction in most cases, if we know

the circumstances. These three features, which may be called the general laws—namely, progressive development, limitation of size and of form by some inherent but not apparent law—are true of the parts of organisms as well as of the whole. Minute investigation reveals part of the machinery by which these results are produced ; viz., in the growth and multiplication of cells. The primordial cell divides and divides again, till the whole has become converted, by the process of segmentation, into a mass of nucleated cells. These embryonic cells become transformed into tissues by further division and proliferation—a process which may be termed histogenesis.

There are, then, two chief stages or periods : the first, cell-multiplication without differentiation ; the second, differentiation with development. In the formation of limbs, the same laws, as was first clearly laid down by John Goodsir, generally prevail. Just as the germinal spot of the ovum is that from which the whole organism derives its origin, so each part, or even each limb, he supposed to have its subsidiary germinal spot or centre of nutrition. Though further observation has shown that this is not strictly true—at least of the higher animals—still each embryonic cell, as it multiplies, bears of course the same relation to its progeny as was borne to it by the germinal spot of the ovum.

The causes of differentiation, like those which regulate size and form, remain obscure. What we know is, that the embryonic cells arrange themselves into certain layers, from which the subsequent development of organs and tissues takes place.

The whole process of development, then, whether of organisms or of parts, may be summed up as being histogenesis by cell-proliferation and multiplication ; the development controlled by certain obscure laws of size and form, and involving constant progression from the general to the special.

On comparing with this process the process of tumour-development, it is impossible to deny the close analogy of the early stages in both, and of the results up to a certain point. In both cases, cell-proliferation and multiplication are the starting-point of growth. Whether, indeed, a tumour starts from a single cell, like the ovum, or from a single germinal centre, as, according to Goodsir, do the limbs and other parts of the body, is uncertain, for the actual beginning of all tumours is concealed from us. When we are able to examine the process, we find germination taking place from many points, but it may, of course, have originated in the first place at one.

The analogy between these processes is, as is well known, the basis

of the Cellular Pathology of Virchow. Confining ourselves to the subject of new growths, we find Virchow laying down the general principle that they all pass through a stage comparable to the undifferentiated cellular stage of the embryo. This is the stage of "indifferent cell-proliferation", in which all the elements are alike, whatever they may be destined ultimately to become. A mass of these indifferent corpuscles he supposes to have a latent possibility of differentiation and development like that of the cells of the embryo ; so that of these elements, which appear quite like one another, some may become epithelium, some cartilage, some bone, and so on.

Indifferent cell-proliferation is an undoubted fact ; we may see it at the margin of almost every growing tumour. Sometimes, considerable masses of a tumour are made up of this, while other portions are more specialised. Nor need we hesitate to allow that, as the earlier stages of all animals have a considerable resemblance in structure, so have the early stages of all tissues. For instance, the Malpighian layer, or rete mucosum of the skin, from which the epidermis is formed, has a structure as "indifferent" as that of granulations or connective hypertrophy, which give rise to vessels and fibrous tissue.

The difficulty is to allow as great a faculty of differentiation to the granulation material as to true embryonic tissue. Is there any distinct evidence that the former ever does give rise, by progressive differentiation, to several kinds of tissue, or that a new growth, composed of several kinds of elements, had its origin in a simple mass of indifferent corpuscles, formed when the organism was already complete ? One line of specialisation can, doubtless, be often traced—are there several ? Virchow has given a categorical answer to this question, and states positively that, in certain tumours, a part of the original elements become converted into connective tissue, another part into epithelium, till a complex structure is produced like that of an organ of the body, *i.e.*, a pathological organ or an organoid tumour, which usually, he says, imitates a gland. Further, he describes a class of "teratoid" or monstrous tumours which represent, not an organ only, but a system of the body, and in which, for instance, there may be skin with both its connective tissue and its epidermis, its sweat-glands and hairs. Such a development is, as he says, not more difficult to conceive than that of simple tissue tumours or organoid tumours ; for, "if there be, in fact, a stage in which there are indifferent elements capable of development in various directions, then it is just as conceivable that they should some-

times develope in one direction, another time in two, as a third time in five or six directions." (*Die Krankhaften Geschwülste*, i, 95.)

And, if these relations were as easy to see in reality as they are to conceive in thought, the case would be clear enough, and we should have no difficulty in recognising the precise analogy between embryonic development and new growth. But, differing with all respect from the great authority of Professor Virchow, we must say that the case is not so clear, for it is doubtful whether either the organoid or the teratoid tumours can be shown to originate in a stage of indifferent granulation-cells. By organoid tumours are chiefly to be understood adenoid or glandular tumours and papillomata, with some cysts. Now, glandular tumours appear to be, in almost every case, outgrowths of existing glands, the few exceptions being certain detached masses of glandular substance near a normal gland, which there is generally much reason to regard as congenital structures; so that, at least, no clear instance can be quoted where the histogenesis of such a tumour from indifferent cell-proliferation has actually been observed. (Lücke, *Geschwülste*, p. 281.) The same may be said of papillomata or their analogues, the polypi of mucous surfaces, which always appear to be either enlargements of pre-existing structures, or else composed of two tissues, namely, vessels and an epithelial covering, which are evidently of different origin, and not differentiated from a common basis. With regard to the only forms of cyst which can be called organoid, those, namely, which contain proliferating structures, these appear to be always either enlargements of pre-existing structures, or else it appears that their epithelial element is really of different origin from the other tissues which they contain.

Finally, the extremely rare structures described as teratoid tumours, in which, for instance, skin, hair, sweat-gland, teeth, or bone, are all found together, appear to be always instances of inclusion of part of the integument at an early period of fœtal life, or else to be comparable to an imperfectly formed fœtus. They are apparently always congenital, with the exception, perhaps, of some growths in the ovaries. When a growth of this kind, originally small, increases rapidly, and is found to contain various tissues, some imperfectly formed and in various degrees of evolution, we cannot doubt that the process of tissue-formation has been actually going on; and, since a considerable proportion of such a tumour always consists of immature or indifferent tissue, it is reasonable to assume that histogenesis has gone on at the expense of this tissue. But in such a case the embryonic mass was formed before, not after, the completion of the organism; so that it must be regarded as part of

the produce of the original conjugation by which the organism was produced.

Such growths are singularly suggestive of the process of budding and agamic reproduction in the lower animals, which are, as Quatrefages (*Metamorphoses of Man and Animals*, translated by Lawson, 1864, p. 238) has pointed out, essentially processes of growth. Waldeyer, indeed, goes so far as to speak of these growths in the ovary as a parthenogenetic development from an ovarial epithelial cell turned into an ovum-cell; and similar productions in the testis have been explained by the presence of ovarial elements, or part of the germinal epithelium in that gland. But tumours quite as complicated occur in distant parts of the body, as the mediastinum (Virchow, *Archiv*, vol. liii, p. 444; Lang, *ibid.*, p. 128).

Other forms of tumour remain to be spoken of, which might be supposed to bear the same interpretation; namely, mixed tumours, such as those composed of partly cartilage, partly fibrous tissue, or partly sarcoma. These undoubtedly pass through a stage of indifferent cell-formation, indifferent tissue being found passing by insensible gradations into each of these forms. Now, in these, all the tissues belong to what is termed the connective-tissue series, or, to use the expression of Virchow, are physiologically interchangeable. We know that one may, under certain circumstances, pass into the other; so that the plurality of tissue-forms need not be taken absolutely as showing plurality of lines of development, or at least the degree of difference is far less significant than in the cases which we have been considering.

One great class of tumours—the true cancers—remains to be considered. Here we find, in general, two types of elements—the stroma, which is a connective-tissue structure; and the cells, which are usually thought to have more or less an epithelial character. If both parts of the structure arise from an indifferent cell-formation, then of course there is a differentiation, or progress from the general to the special, quite comparable to that of embryonic development. Whether it is really so, will be discussed hereafter. At present, we may take it provisionally as not proved, and conclude that indifferent cell-formation does occur in the early stages of cancer, but that it is not certain whether that does or does not produce the epithelial elements.

From all this we must conclude that the process of tumour-formation is strictly analogous to that of embryonic development up to a certain point—namely, so far as both processes result in the formation of a mass of indifferent or similar cells, such as the mulberry-mass of the embryo,

or the indifferent granulation-material of new growths. Beyond this, the parallel is less exact, and the progressive differentiation which is characteristic of embryonic development is less clearly traceable in tumours. The indifferent granulation-material, which is analogous to the undifferentiated embryonic structure, is capable of producing structures which vary within certain limits, such as the group of connective tissues, or, on the other hand, of producing epithelial elements; but it is uncertain whether the same group of cells can produce both.

One very striking coincidence may be noticed with regard to the point at which the resemblance ceases to be exact; viz., that the early stage of development of the ovum—that which is imitated by new growth—is possible, and perhaps even in some animals the rule, without impregnation. This amount of development is possible to elements derived from one organism alone, though conjugation with elements derived from another is necessary to establish the progressive differentiation which results in the development of a complex structure. We may, therefore, say that what amount of development an unimpregnated ovum is capable of, that, at least, is possible to new growths, which may imitate on the one hand the incomplete process of development of such ova in the higher animals, and on the other hand, in rare cases, make some approach to repeating the agamic reproduction of the lower animals.

Comparison of Tumour-Growth with Repair and Reproduction of Lost Parts and with Inflammation.

It is well known that the capacity for reproducing lost parts differs very greatly in the animal kingdom; and, while it is generally greater in the lower than the higher animals, the differences are not entirely to be so explained. The most general law which seems to have been arrived at is this, that the capability of repair is inversely as the amount of metamorphosis or change through which the animal has gone. Insects, for instance, have no power of restoring lost parts; batrachia have a great deal. In the mammalia, at all events, this power is extremely limited. An organ once lost is lost irretrievably; and even the more specialised tissues, as muscle and ganglionic nervous matter, are usually replaced by other tissues, not actually restored. These very tissues, it is worth notice, rarely or never appear in new growths. New growth, taken as a whole, has, perhaps, greater possibilities than has the process which constitutes repair—giving rise to more various and more specialised products. On the other hand, the latter process is far more completely subject to the

general law of evolution of the whole organism, for the parts reproduced always conform to the size and shape of the whole body; while it is, of course, the most remarkable feature of new growths, that they are so entirely unlimited in these respects. In other respects, the reproduction of lost limbs in some of the lower animals, has a decided analogy to the production of a tumour. Harry Goodsir (*Anatomical and Physiological Observations*, 1845) described, for instance, long ago, the reproduction of a claw in the crustacea, as starting from one nucleated cell, which multiplies and gives rise to other centres of growth. In fact, there is a true cell-proliferation.

With regard to the minute processes of repair, they differ from the corresponding processes in new growth very greatly, in the degree to which the vessels and the blood with its formed elements participate therein. The share taken by vascular changes in ordinary repair is known to be very great; so much so, that it has been the great question with surgeons, whether the healing of wounds is possible without inflammation. In new growth, vascular phenomena seem to play a subordinate part, though perhaps their importance has been underrated. At all events, in order to compare the one with the other, we must leave out of account the vascular changes; and then we find that the residue, or changes in the fixed tissues in repair, bear the closest analogy to new growth, being really, in the early stages, processes of germination and proliferation. These, of course, are also the tissue changes in early stages of inflammation, with which repair is so intimately connected. In describing one, we are, therefore, describing the other. Of course, the extent of these germinative changes is a matter of much controversy; and I am, therefore, glad to be able to show you the results of some direct observations.

As an instance, we may take the changes produced in an extremely simple structure, such as the omentum, by inflammation and by new growth respectively.

It is well known that mechanical injury, heat, and the action of various irritating substances, all give rise to the same series of changes called inflammatory. We may, then, take any one of these as a type of the rest. I have accordingly represented on the diagram the appearance of a human omentum inflamed in consequence of perforation of the bowel. The endothelial cells covering the fibrous trabeculæ are seen in several places to give evidence of proliferation; that is to say, one sees divided cells, cells with divided nuclei, groups of cells showing by their shape that they have been formed under mutual pressure, and, therefore,

probably from one original mass ; and also what look like compound, or mother cells.

These are the evidences of tissue-germination, and agree with the observations of Stricker, Burdon Sanderson, and others, on the cornea. They also resemble the phenomena brought to light by the comprehensive researches of Dr. Klein on the serous cavities of animals in which he has found germinating endothelium. Now, in the early stages of three different new growths—namely, cancer, sarcoma, and tubercle—we see the same or similar proliferative changes, sometimes affecting the endothelium, sometimes the connective tissue. Without now dwelling on other peculiarities of these minute changes, it will be enough to have shown that in the early stages of all these growths there is actual germination of the tissues, and that the same is to be seen in inflammation. The appearances of inflammation in connective tissue are still more like those of certain stages of new growth. The diagram, for instance, representing indifferent cell-proliferation, might equally well stand for one of inflammation. At the same time, I must venture again to lay stress upon the immense preponderance, in the latter process, of phenomena connected with the vessels and blood-corpuscles, which are only subsidiary in the case of new growths. We know, moreover, that even the resemblances are only like the resemblance between all embryonic tissues, for instance; it is a resemblance involving great latent possibilities of difference.

Products of the Reparative Process.—If we pass to the more definite structures produced by the process of repair, we still see a considerable analogy between them and new growths. The repair of many tissues passes through a stage very fairly comparable to what we called the indifferent cell-proliferation of new growths. Granulations are tumours in everything but in permanence. It is unnecessary to describe their structure minutely. Essentially outgrowths of vessels, they possess a framework or stroma which, except in its extreme vascularity, is not unlike that of a lymphatic gland, and to which histologists have not always done justice; and, beside, we have a large number of lymphoid corpuscles. The structure has been compared to that of a round-celled sarcoma, but in reality it is only the cells that are alike ; the architectum of the growth is very different. It might rather be called, in the nomenclature of new growths, a highly vascular fibroma, with very numerous migratory cells. But, as we know, this condition is far from permanent. Granulations either die away or else they lose their abundance of lymphoid cells; the fibrous element increases; and they become

organised, as it is said, into fibrous connective tissue and similar tissues. Do they also become organised into epidermis? We know that some epidermis commonly covers them; and, according to the more generally accepted view, this is produced by metamorphoses of some of the lymphoid or indifferent cells. Some authorities, again, regard the epidermis as of different origin; and the question is so undecided, that we must hesitate to pronounce an opinion. The only point on which we must insist is that, both positively and negatively, these results agree perfectly with what we said just now about the indifferent cell-proliferation. The question of the origin of all epithelium produced for purposes of repair is one which I prefer to consider in the next lecture.

So far, then, as we are able to compare the phenomena of repair and inflammation with those of new growth, there are important analogies; but a large part of the phenomena of the two former processes—those, namely, connected with the vessels, exudation and cell-migration—have not, so far as is yet known, their parallel in the development of tumours, except as simply subsidiary to the germinative changes.

Comparison of Tumour-growth with Hypertrophy and Hyperplasia.

THE formation of new growths has, doubtless, many points of contact with the process by which existing parts of the body are increased in size. In the first place, those tissues or parts of the body which are specially disposed to hypertrophy are, with certain exceptions, also very liable to become the seat of tumours. For instance, no tissue is so constantly liable to hypertrophy as the adipose; and precisely here do we find very common and sometimes enormously large tumours. No doubt, the increasing skill and confidence of surgeons has made extremely large tumours less common of late years; but the largest tumour (so far as I know) on record is a fatty tumour, of which a drawing is preserved in the museum of the Harvard University at Boston. The description of it may be not without interest.

An enlarged drawing of a woman, in whom there was formed a tumour that was, perhaps, as large as any that has ever been recorded. The estimated weight of the tumour alone, at the time of her death, was not far from 275 lbs., and the weight of the patient without it was probably not 100 lbs. The age of the patient at the time of her death, in 1854, was 36 years. In 1838, being then in the sixth month of her first pregnancy, she was kicked in the right iliac region by a cow, and to this accident she always referred her troubles. She, however, went her full time, and was confined in June, suffering afterwards habitually from

soreness of the side and weakness in the loins. In September, 1840, a second child was born. Six weeks before labour, she lifted a heavy kettle, swooned, and, on recovery, found a small tumour protruding from the vagina. Her health was delicate for the next eleven months. In 1841, she aborted at the third month, after a fright. Three days afterwards, she took cold, and had tenderness and fulness of the abdomen, the right side becoming so sensitive that the bed-clothes were oppressive.

In 1843, a dead child was born at the full period, and after a severe labour. The vaginal tumour at this time projected three or four inches beyond the labia, was one inch and a half to two inches in diameter, and its attachment was beyond the reach of the finger. Subsequently to this labour, the whole tumour sloughed off. Difficulty of passing the urine also followed, and the catheter was used for some months. During this attack, a soft immovable tumour was felt a little to the right of the linea alba, and almost filling the right side of the abdomen, and from that time the abdomen enlarged pretty rapidly for a year.

About four years after the tumour appeared in the abdomen, another showed itself in the right labium, extending to the nates. This last was soft and elastic, and, for a year or two, it could be returned within the pelvis or abdomen; but, subsequently, it enlarged *paripassu* with the abdominal tumour, and both fluctuated so distinctly that the case was thought to be one of dropsy. The tumours were tapped or incised eight times, but no fluid was discharged. The abdominal tumour had produced the most distressing dyspnœa, so that she could scarcely breathe except when on her hands and knees. As the tumour of the hip enlarged, however, the dyspnœa was relieved, as well as the general anasarca, and a numbness of the lower extremities, from which she had suffered much. At the urgent solicitation of the patient, the tumour upon the hip was opened and the finger passed in, but a soft tissue only was felt, very much like the omentum.

After the relief above referred to, the patient's health improved. She again became pregnant, and, in 1848, was delivered at the full period, artificial means being required, and the child dying during the labour. When this was over, she returned to her former condition.

Before this last pregnancy, when she was in a sitting posture, which she sometimes attempted, the abdominal tumour rested upon her thighs and as far as her knees; there being no marked increase of size before delivery, nor diminution afterwards. The tumour of the hip was fifteen inches long, ten inches in diameter at its longest part, and four inches in

diameter at the point of its connection with the perineo-ischiatic region.

About 1850, the patient weighed, on a platform-scale, 269 lbs. Her greatest weight before marriage, and when in full health, was 108 lbs.; and, her flesh being very much reduced, her own weight was estimated, at the above date, at 90 lbs., and that of the tumour at 179 lbs. From this time, or from the year before, she was confined entirely to her bed as long as she lived.

In June 1851, when Dr. Buckner saw her, the circumference of the abdomen was 7 ft. 8 in., and the distance from the ensiform cartilage to the pubes 3 ft. 6 in.; the form of the abdominal tumour being regular and very prominent, so that the outline, if continued, would be rather ovoid than round. The tumour of the hip extended along the thigh, and measured 2 ft. 6 in. in length and 18 in. transversely. The circumference, longitudinally, was 4 ft., and that of the neck of the tumour was 2 ft. 2 in. It was of a regular, elongated form, and considerably larger at the upper extremity than the lower. Some slight mammillary elevations, however, existed upon the surface, but these were subsequently found not to differ from the rest of the tumour in structure.

During the last year of the patient's life, there was frequently a pustular eruption upon the surface of the posterior or ischiatic tumour, leading to superficial ulceration; but this would in time dry up and heal. With this exception, and those already referred to, her general health was usually good, and her functions were well performed; menstruation being regular as to time and quantity, though painful during the last few years. Towards the close of 1853, the cutaneous affection increased, her health failed, and she died in January 1854.

A necropsy could not be had; but Dr. Smith, in order to get the body into something like a coffin, removed the ischiatic tumour in the presence of her husband. Within it was a cavity into which he passed his arm to above the elbow. The arm was then passed to about the same extent upward into the pelvis and abdomen; and, with the other hand upon the tumour externally, Dr. Smith satisfied himself that the abdominal viscera were intact, and that the tumour was external to the peritoneal cavity. The two cavities contained eight pints of fluid; the one in the ischiatic tumour being evidently, in the opinion of Dr. Smith, a process from that of the peritoneum; and the two tumours, though entirely distinct externally, being portions of one and the same growth. The communication between the peritoneal cavity and the prolongation from it he believed to be through the sacro-sciatic notch; but to this

view of the case Professor Delamater thought that there were objections. The ischiatic tumour consisted mainly of a soft adipose structure, interspersed with delicate layers of fibrous tissue; and, in bulk, the tumour was large enough to fill a common wash-tub. After the removal of the tumour, the genital organs and the anus, which were fully in view, were found to be somewhat drawn to one side, but otherwise unchanged. The abdominal tumour was not examined; but there can be no doubt, as Professor Delamater remarked, that it was mainly adipose. Professor Delamater finally remarks, that "the continued growth of these tumours was unabated to the end"; and, basing his computation on the above estimated weight of the tumour, he says "we shall get 268⅝ lbs. as the ultimate of the solid and fluid constituents of these abnormal productions. Drs. Johns and Beach estimate the entire weight at 275 lbs., which I have no doubt is within the truth". (*Catalogue of the Warren Anatomical Museum*, p. 642. Boston: 1870.)

The tumour admirably illustrates several of the laws of new growths, which we have endeavoured to trace. It arose in a tissue specially disposed to hypertrophy, in a part of the body where hypertrophy of this tissue is particularly liable to occur, as witness the extraordinary development of the Hottentot women; and from its causing absolute rest, even the ordinary waste of fatty tissue was reduced to a minimum. These conditions do not certainly at all explain the gigantic development, but they must be regarded as subsidiary causes.

Again, we sometimes see that even the special parts of organs which are liable to hypertrophy are also liable to become the seat of new growth. In the skeleton, for instance, a remarkable proclivity to disease is observed in the long bones at the termination of the shaft, or close to the junction of the epiphysis.* This is the portion which becomes enlarged in rickets, and it is also the most frequent situation for tumours. Some remarkable cases of multiple exostoses growing from these parts of the skeleton are on record; and as they illustrate in a striking manner the transition from overgrowth to new growth, one may be worth quoting. It has been published by my friend, Mr. Arnott, in the *Pathological Transactions* for 1872.

A girl, aged 18, in good health, observed a small swelling on the

* Virchow gives, as the usual position of cartilaginous exostoses, the upper end of the tibia and the lower end of the femur. In this case he suggests that the growth may come from the residual cartilage between the bone and the epiphysis, as most of these growths occur in young persons; but this would not explain the equally common occurrence of bony exostoses at the same parts. (*Die Krankhaften Geschwülste*, ii, 14.)

inner side of the knee, which was found to be a bony growth, of the size of a large hazel-nut, springing from the ridge leading to the internal condyle of the femur. On closer examination, similar tumours were found on the other side of the lower end of the bone, and in symmetrical situations on all the long bones of the leg. The patient died of the consequences of an operation to remove one of these tumours; and we had the opportunity of examining the skeleton. At the *post mortem* examination, I particularly noticed the situation of the extremely numerous exostoses, which grew from nearly every bone of the body. So far as could be traced, the skull, sternum, hands, and feet were free; but each of the long bones of the extremities had one or several growths springing from the typical situation which I have already indicated; that is, near the extremity, and close to the epiphysial junction. Each rib had similar growths in two situations, namely, near the costal cartilage in front, and near the head and tuberosity behind. The lateral processes of the lumbar vertebræ exhibited similar outgrowths, which were also found upon the sides of the vertebræ, and on several symmetrical parts of the pelvic bones.

Now, the overgrowth of bone here was so general, and so conspicuously confined to the typical situations in which general hypertrophy is seen, that it is surely not too much to regard the process as one which would have appeared as simple enlargement, had the bones been soft as they are at the time of life when rickets occurs. The question of rickets was raised, at the discussion which took place on this case, at the Pathological Society, and the obvious analogy was pointed out; at the same time, there was a general agreement that it could not be a case of this disease. Looking, however, at the very general distribution of the disease; at the fact that the red medulla of the spongy bone, which formed great part of the outgrowths, is probably concerned with blood-formation, and certainly has intimate relations with the general nutrition of the body, it is impossible not to see that there was a general disease, or condition of the body, of which the local disease was the manifestation. We may also remember that the age of the patient was just that at which the ossification of the epiphyses of the long bones, and that of the head and tuberosity of the ribs, takes places. This is a perfect example of the constitutional character of certain tumours, and of the absolutely imperceptible transition from hypertrophy to new growth.

In Mr. Arnott's words, "the tumours appear to be only exaggeration of normal development, at a time when it is at its acme of activity, by which the bones, during a sudden increase of growth, sprout out

into fantastic displays of such growth." I confess I should describe this case as hypertrophy rather than new growth, thinking that the definite and peculiar form of the enlargements was due to the unequal resistance of the parts.

Lest I should be thought to have trespassed unduly on the field of the surgeon, let me select a very similar instance from among the diseases which traditional usage has assigned to our care. Enlargement of the lymphatic glands is well known to be an extremely common affection of the body, more especially during the period of growth, and this enlargement is sometimes merely transitory, sometimes chronic. The structure of the glands, thus enlarged, is not generally different from that of the normal glands. In another class of cases we have enlarged glands, in outward appearance, the same as these, but nevertheless differing, both in their minute structure and in their history. Either the newly-formed gland-tissue, by which hypertrophy is effected, is found to have an inadequate vitality, so that it speedily decays and becomes necrotic, in which case we call the change scrofulous; or else the newly-formed gland-tissue becomes hard, loses some of its cellular elements, and shows increase of the fibrous element between the cells, till there results a change, recognisable by external characters, as induration; and, by its minute anatomy, as increase of the intercellular substance, or stroma. These two conditions—scrofulous change and induration—are the ultimate stages of chronic enlargement, or hypertrophy, from which, to them, there is a perfectly gradual transition, and at particular stages of the disease it would be impossible to say, with certainty, what name ought to be applied. Whether the ultimate difference depends upon difference in the original structure of the body, or upon nutrition, or upon external influences, we are rarely able to say.

In all these cases the form of the gland is not altered, and it would be only by a somewhat strained use of terms that we could describe the enlarged organs as tumours. Let us now go a step further, and consider those cases in which the glands are not only enlarged, but in which, by thickening or inflammation of their capsules, and the connective tissue around them (periadenitis), the group of glands becomes adherent together, and a lobular mass is formed, which not only possesses sufficient physical coherence to be regarded as a definite tumour, but also has evidently a certain physiological unity, being subject to the same laws of morbid growth. Is it possible to avoid calling this a tumour, or new growth? Certainly, in the present state of science, every one would call this a lymphoma, while we should call an enlarged

gland simply a case of hypertrophy. Yet it is quite certain that our powers of observation, at least, do not permit us to draw any line between the two. Nor is there, as I believe, any anatomical difference. One supposed distinction is the presence, in some cases, of peculiar elements—myeloid, or giant-cells—but these elements are found in many, if not in most, simply hyperplastic conditions of lymphatic glands. (*Transactions of the Pathological Society*, vol. xix, p. 401, 1868.)

If we now go a step further, and examine another class of cases, we shall find that, in specimens not differing very greatly from those last mentioned, the enlarged glands are in a direct connection with masses of newly formed tissue around them, more distinct and prominent than the thickening of the capsule. These masses of newly formed tissue penetrate or infiltrate the neighbouring parts, and, so far as they reach, convert them into similar structure. This is, of course, not a case of adenitis, or periadenitis, but of an infective, or what is generally called malignant, tumour. Nevertheless, there are such cases, in which the structure of these adventitious masses differs little, if at all, from that of certain parts of healthy lymphatic glands (*Transactions of the Pathological Society*, vol. xxiii, p. 248, 1872): so that what is anatomically a kind of hypertrophy becomes, in its mode of extension, an actual new growth, and, in its effect on the body, malignant or infective. Lymphatic structure may, however, show another peculiar mode of occurrence which, nevertheless, we cannot but call hypertrophy. That is to say, the tissue, similar to that of lymphatic glands in other parts of the body, may also be increased. Take the case recorded by Dr. Moxon in the *Transactions of the Pathological Society* (vol. xx, p. 369, 1869), which is a type of numerous others, where growths of similar anatomical structure were found to occur simultaneously in the lymphatic glands, spleen, tonsils, and follicles at the base of the tongue. All these parts contain normally the same tissue, viz., that which is called cytogenous connective tissue, or adenoid tissue, and the occurrence of masses of the same kind in all may then be considered as a hypertrophy. In Dr. Moxon's words:—

"The disease of these organs is the same in all, consisting of a new formation, which resembles the lymphatic gland tissue, but that the elements were larger in size. The relation of the disease to the structure and function of the parts affected, plainly points it out as constitutional; by constitutional, I mean belonging to the parts in their relation to the other tissues; in other words, pertaining to their nature and use in the economy. So far, the case is parallel to the not uncommon occurrences of multiple melanoses of the skin, or multiple cancers of

bone, either of which examples will give us instances of malignant disease attacking at many points the same system of tissues, and that under such circumstances that we cannot suppose the tumours to have spread from any one of the diseased spots to the rest by infection or transplantation."

I would only remark that, while agreeing with Dr. Moxon's interpretation of the simultaneous occurrence of the growths in similar, not identical organs, I wish also to lay stress on the fact of the growth being, in all cases, presumably a hypertrophy, and quite as justly comparable to the multiple exostoses just mentioned as to multiple cancers; though in this case there was also infection of the contiguous part of the lung, so that it was infective or infiltrating, as well as multiple or generalised.

These instances may suffice to show that hypertrophy may give rise to products which resemble the most pronounced form of new growth in their distinctness, or their generalisation, and even in their infectiveness.

I would further point out, that tumour-production is like hypertrophy in other respects, viz., that both processes occur with a certain frequency in particular organs, as well as in particular tissues. This is, however, true only of organs that are subject to certain kinds of hypertrophy. It is not functional hypertrophy, that is to say, such as hypertrophy of the heart and muscles. It might be enough to say that the striated muscular tissue is one not at all disposed to new growth; but then the question would arise, Why should it not be so? This may, I think, be answered in two ways, viz., either by the principle stated just now, that expenditure of force is antagonistic to excessive growth, or that highly specialised tissues have little germinative power; but it is enough to see that, when hypertrophy is produced by functional activity (whatever the mechanism may be), it will be proportional to functional activity, and there will be no surplus for abnormal growth. But there is another form of enlargement, which I should like to call nutritive hypertrophy, were it not that, if the word hypertrophy be taken in its original sense, the expression is tautology. What I mean is, overgrowth dependent on nutrition, not on function. Uncomplicated instances of this are very rare; but it is singular that the most extraordinary instance on record of hypertrophy of the heart is of this kind, viz., that in the museum of St. George's Hospital, which weighed over four pounds, and where no cause of obstruction was discernible; but it is more constantly the case in such hypertrophies, for instance, as that

of the thyroid gland, a part which is frequently the seat of new growth, as distinguished from enlargement.

Also, it is most strikingly true, that those parts which are subject to occasional or periodical enlargement, or on which the overgrowth is consequent to change, perhaps functional, in some other organ. Take, for instance, the uterus and mammary gland in women.

Whatever the mechanism may be, there is no doubt some mechanism by which these parts are especially disposed to abnormally rapid nutrition and activity of growth under particular circumstances. This machinery will, we know, from time to time, act blindly. The uterus will enlarge around a tumour, or a mole, and finally contract upon it, as in parturition; and the mammæ will often enlarge sympathetically with various affections of the uterus, not necessarily with pregnancy. (*Lee's Lectures on Midwifery*, p. 169.) Can we doubt that some disordered action of this mechanism is an important factor in the production of tumours in these parts, and that the remarkable frequency of new growths in the mammæ and uterus is partly thus to be explained?

Before leaving the subject of hypertrophy, it will be desirable to inquire what are the minute changes by which the increase of parts is effected, and whether these are comparable to those which are concerned in embryonic development, and in the production of tumours. Enlargement of organs appears to be partly effected by increase in size of the elementary parts, and partly by multiplication of these parts. The latter, or hyperplasia, is no doubt the more important process when the overgrowth is considerable.

It is a little difficult to get direct evidence of the minute changes; but in one of the commonest instances, hyperplasia of connective tissue, or fibrous induration, it is quite evident that the first step is the multiplication of nuclei; and the proliferation of connective tissue thus resulting is an important factor in many diseases.

In order to exhibit a very similar process in another part of the body, I will recur to the point which was touched upon just now, the structure of the omentum. The human omentum is a structure which undergoes considerable, though very gradual, changes as life goes on. As is well known, we comparatively rarely find, in elderly persons, an omentum as thin and pellucid as that of children. It becomes thicker, shorter, and often adherent to neighbouring parts, while adhesions are also formed between the parts of the membrane itself. When minutely examined, it is found that these changes are twofold. On the one hand,

the amount of homogeneous intercellular substance contained in this membrane in early life becomes diminished, the fibrous element increases, and fibrous outgrowths are formed which effect adhesions and contractions of distant parts. It therefore becomes completely fenestrated as life advances, while, at the same time, the fibrous bundles are actually stronger and thicker. Minute examination reveals, even in perfectly normal structures, some of the ultimate changes connected with these transformations. We see what I have represented in the diagram (Fig. 1). Here may be noticed a comparatively large amount

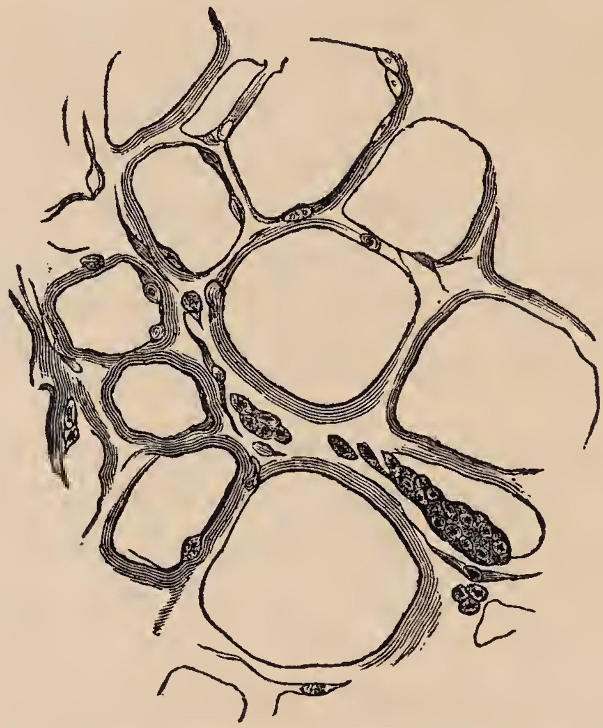

Fig. 1.—Apparently healthy Human Omentum, shewing elongated connective-tissue cells, and masses of germinating endothelium ; groups of three, four, or more nuclei, surrounded by some protoplasm. Magnified about 250 diameters.

of intercellular substance, a few connective tissue corpuscles, and besides, many cells and groups of cells attached to the outside of the fibrous bundles. These represent the endothelium or serous epithelium of the surface, but of course only in part. The conditions under which these structures are examined in the human body prevent us from getting these structures, so liable to decay, in a perfect state, and from applying the most satisfactory process for their demonstration, viz., nitrate of silver, since this only acts properly on quite fresh tissues. But what can be seen is enough to show in the normal structure phenomena of germination quite comparable to those involved in the processes of inflammation, tubercle, and new growth. Dr. Klein has shown the same thing much more completely in the serous membranes of animals, and regards the process as one strictly normal.

Compare with this the appearances shown in the diagram (Fig. 2) representing the early stage in a minute secondary sarcomatous growth

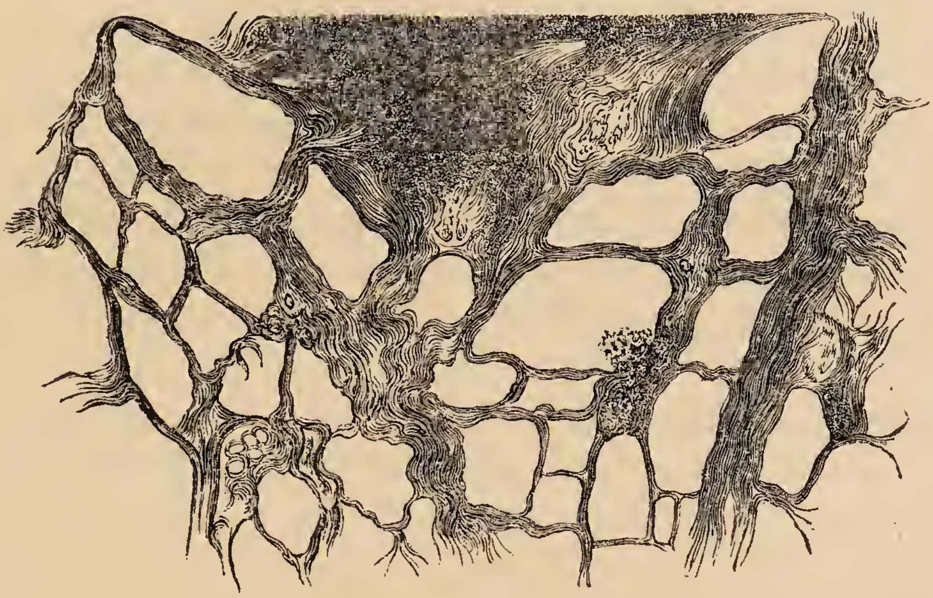

Fig. 2.—Portion of Human Omentum, shewing one larger and two smaller sarcomatous tumours in an early stage. Magnified about 80 diameters.

of the omentum of a child. It was a case in which the rupture of a cystic sarcoma into the peritoneum set up a large number of small secondary growths, which appeared superficial and were easily detached. In Fig. 3, one of these is shown more highly magnified, and is seen to

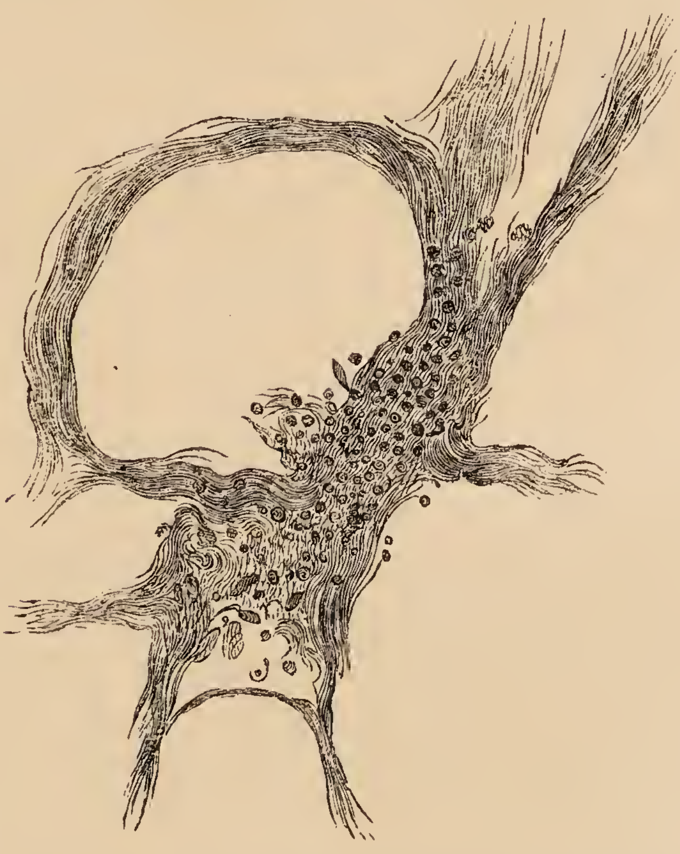

Fig. 3.—Portion of Fig. 2 more highly magnified, shewing a minute sarcomatous tumour arising wholly by multiplication of small cells. Magnified 250 diameters.

be made up merely of a mass of simple elements, cells, or nuclei. Other parts of the same preparation gave more distinct evidence of germination in the elements, connective tissue or endothelial, of the part.

I conclude, then, that a hyperplastic process is one of the chief factors in hypertrophy, in the embryonic development, in repair and inflammation, as it is in the growth of tumours. It would also appear that the element common to all these processes is one which is also a normal one in certain parts at least of the human body, and connected with the chronic processes by which certain fundamental changes are effected in it.

New growth, then, is distinguished from the other processes just referred to—embryonic development, repair, inflammation, and hypertrophy—not by its minute characters, but by what may be called figuratively its direction and end, or by its relation to the rest of the organism; and the physiological factor which is common to all these processes, far from being strange or alien to the soil, is probably even a part of the normal life of the body.